REMARKS

As indicated in the reply dated December 4, 2009 in connection with the subject application, Applicant is submitting this Supplemental Reply in support of the present invention after the accompanying Wade et al. data was publicly presented on December 9, 2009.

In further support of the non-obviousness of the present invention, the attached Wade et al. 2009 abstract reports that a very low daily dose of pipamperone (5 mg) added to the selective serotonin re-uptake inhibitor citalopram (40 mg) provided superior antidepressant effects and less discontinuations compared with citalopram alone. In contrast, treatments with atypical antipsychotics are known to be associated with increased risk of discontinuation due to adverse events (see, e.g., meta-analysis by Nelson et al. 2009 in SIDS submitted on December 2, 2009).

No fee is deemed necessary in connection with the filing of this Supplemental reply. However, if any fee is required to preserve the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

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Dated: December 10, 2009
New York, New York

By /Alan D. Miller/
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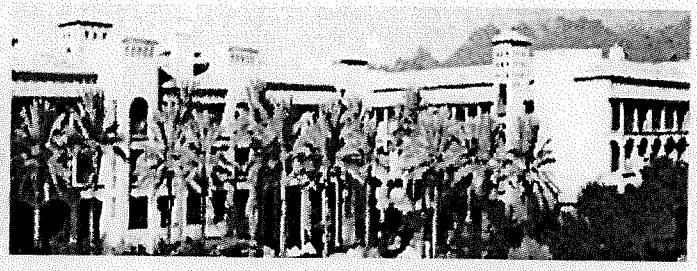

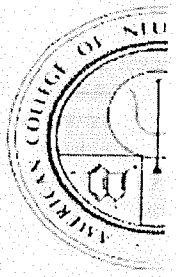

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Addition of a Selective 5-HT_{2A}/D_4 Antagonist Accelerates the Antidepressant Effects of Citalopram

Author Block: *Alan G. Wade, Charles Nemeroff, Alan F. Schatzberg, Thomas E. Schlaepfer, Ludo Haazen, Erik Buntinx.* CPS Research Ltd, Glasgow, United Kingdom

Abstract:

Improvement in symptoms of depression is typically delayed with antidepressant treatment, and that delay is associated with prolonged morbidity, increased risk for suicide and substance abuse, decreased compliance, and early treatment discontinuation. One theory for the delay in clinical response is that stimulation of $5HT_{2A}$ receptors induces a temporary feedback loop reducing the effect of increased serotonin at the synapse. This raises the possibility of increasing the early efficacy of selective serotonin reuptake inhibitors (SSRIs) by blocking this mechanism. Pipamperone (PIP) at very low doses acts as a highly selective $5HT_{2A}$/D_4 receptor antagonist. The purpose of this 8-week, double-blind, parallel-group, single-dummy study was to investigate whether the addition of PIP 5 mg bid to citalopram (CIT) 40 mg daily would increase the rate of resolution of depressive symptoms.

The mean total MADRS score (±SD) of the 165 patients (81% women; mean age, 40 y; mean body weight, 80 kg) was 32.6±5.5. More CIT than PIPCIT patients discontinued treatment in the first 4 weeks [15 (18%) vs 3 (4%); *P*=0.003].

Reductions in mean total MADRS scores were significantly (ITT LOCF) larger in patients receiving PIPCIT after 1 week [-6.42±6.18 vs -3.99±5.15; *P*=0.007] and 4 weeks [-15.06±8.48 vs -12.11±8.30; *P*=0.025] compared with those receiving CIT alone. Significant differences in favor of PIPCIT were observed in MADRS items "reduced sleep," "reduced appetite," "concentration difficulties," and "pessimistic thoughts." Mean CGI-I scores were also improved after 1 week of PIPCIT [3.09±0.85 vs. 3.47±0.72; *P*=0.002]. There were no significant differences observed at 8 weeks. No additional, clinically significant adverse events were noted in the PIPCIT group.

A very low dose of PIP added to CIT provided superior antidepressant effects and less discontinuations compared with CIT alone during the first 4 weeks of treatment, and especially in the first week, at apparently no tolerability/safety cost.

Author Disclosure Information: **A. Wade**, None; **C. Nemeroff**, None; **A. Schatzberg**, None; **T. Schlaepfer**, None; **L. Haazen**, PharmaNeuroBoost, *Part 5*; **E. Buntinx**, PharmaNeuroBoost, *Part 5*.

Category (Complete):
: Pharmacology: clinical
: Mood disorders

Keyword (Complete): Depression, Unipolar / Bipolar ; Clinical Pharmacology / Clinical Trials ; Serotonin ; Psychopharmacology
Sponsor (Complete):
Please select either YES or NO: NO
ACNP member sponsor name: : Alan F. Schatzberg
Member sponsor email address: : afschatz@stanford.edu

Hot Topic (Complete):
Please consider my abstract for hot topics (Required)
: No
If yes, please classify your abstract from the selection below:
Clinical

Status: Complete

Alan Miller

From: Opgeslagen met Windows Internet Explorer 8
Sent: Monday, October 05, 2009 7:40 AM
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Dear Alan G. Wade:

Congratulations! Your poster has been accepted for presentation at the 48th ACNP Annual Meeting in Hollywood, Florida, December 6-10, 2009. All three poster sessions will be held in Great Hall 1 & 2 of the Westin Diplomat Resort and Spa. An informal reception will accompany each session.

Session I Monday, December 7th, 5:30 p.m. - 7:30 p.m.
Session II Tuesday, December 8th, 5:30 p.m. - 7:30 p.m.
Session III Wednesday, December 9th, 5:30 p.m. - 7:30 p.m.

Your poster, "**Addition of a Selective 5-HT_{2A}/D_4 Antagonist Accelerates the Antidepressant Effects of Citalopram,**" has been scheduled for presentation on **12/9/2009 5:30:00 PM** on Board Number **188**. The presenting author must attend the poster during its designated session. A copy of the abstract, typed in large letters, should be posted on the upper left-hand corner under the title, along with the sponsor's name, if applicable. The poster may cover an area up to 4 feet high by 6 feet wide. The boards are constructed so that poster material will be at eye level. Push pins or thumbtacks must be supplied by the poster presenter. The ACNP will only have a limited supply of pushpins.

Posters have been grouped by topic whenever possible. Please be sure to mount your poster on the board that has your assigned number. Posters should be mounted by 10:30 a.m. on the day of your designated session. They should be removed no later than 8:00 p.m. on the same day. Posters that are still mounted after 8:00 p.m. will be discarded.

Complete disclosure information for all authors must be included on the lower right hand side of the poster board.

Industry authors must list their employer as a conflict on the poster board.

Poster presenters must be willing to reveal the structure of a compound or gene discussed during their presentation.

Poster abstracts are not archival. They do not bear the imprimatur of the ACNP and are not to be cited or referenced. As the poster author, you should be contacted for appropriate reference for citation.

The ACNP is giving all poster presenters the opportunity to share your poster with those ACNP members and 2009 meeting attendees who did not have the opportunity to see your poster during the sessions. An E-Poster website has been created for you to upload and share your poster. You will be sent a separate email with instructions for this.

The American College of Neuropsychopharmacology does not allow the use of its name, logo, or the annual meeting name in association with any press release, CME activity, or any other public use unless approval is granted by the College. This includes all press releases, whether from academic institutions or from industry. If you want to ask for permission to issue a press release that mentions the ACNP Annual Meeting, please contact Sarah Timm at stimm@acnp.org. She will have your press release reviewed by the Public Information Committee and by Council if necessary.

If your poster was considered for a Hot Topic, and is selected, you will be notified.

Below is a list of suggestions for mounting your poster. If you have any questions, please contact the ACNP Executive Office at 615-324-2360.

POSTER PRESENTATION & MOUNTING SUGGESTIONS

2009 ACNP ANNUAL MEETING

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2. Place the poster title at the top of the poster board in 1" high letters.
3. A copy of the abstract, typed in large letters, should be posted on the upper left-hand corner under the title, along with the sponsor's name, if applicable.
4. Disclosure information for all authors must be posted on the lower right-hand side.
5. Hand-lettered materials should contain appropriately heavy lettering at least 3/8" high. Shade block letters where possible.
6. Remember that illustrations may be read by interested scientists from distances of about 3 feet or more. Keep them simple. Charts, drawings, and illustrations should be heavily drawn.
7. Do not mount materials on heavy board because it will be difficult to affix the materials to the poster board. Keep presentation as lightweight as possible.
8. Prepare and bring to the meeting all materials needed for the poster (figures, tables, etc.).
9. Bring the necessary pushpins or thumbtacks to mount the poster. The ACNP will have a limited supply of pushpins.

*NOTE: The mounting surface for 2009 posters will require PUSHPINS or THUMBTACKS.

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